RENAL DYSFUNCTION AND ACCELERATION OF CORONARY DISEASE

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The first world pandemic of obesity is driving secondary epidemics of type 2 diabetes, dysmetabolic syndrome, and hypertension. This results in increasing numbers of patients with renal disease and coronary atherosclerosis. Chronic kidney disease (CKD) accelerates the course of coronary artery disease, independent of conventional cardiac risk factors. In addition, CKD has been shown to confer inferior clinical outcomes following successful coronary revascularisation, which may be offset by arterial grafting. This article reviews the evidence for accelerated cardiovascular disease in the presence of renal disease with reference to new diagnostic and therapeutic targets.

ACCELERATED ATHEROGENESIS IN CHRONIC KIDNEY DISEASE

Tens of millions of persons worldwide have combined cardiovascular disease (CVD) and CKD.[1] In the USA alone, over 300 000 individuals are on renal replacement therapy (RRT),[2] which confers a five- to 40-fold increased risk of fatal cardiovascular events.[3 w1 w2] CKD is commonly defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, or the presence of a raised urinary albumin to creatinine ratio > 30 mg/g on a spot urine sample. Although conventional risk factors such as hypertension, diabetes mellitus, and dyslipidaemia are commonly associated with CKD and its attendant long term CVD morbidity, these risk factors alone do not fully explain the prevalence of CVD in this population.[4] Figure 1 depicts the independent and dominant effect of renal disease on coronary heart disease death rates among diabetics. Novel risk factors such as homocysteinaemia (Hcy), raised lipoprotein Lp(a), oxidative stress, endothelial dysfunction, diminished transforming growth factor β1 (TGF-β1), chronic inflammation, and vascular calcification are increasingly linked to accelerated rates of atherogenesis in the setting of CKD. Furthermore, patients with CKD have inferior clinical outcomes following percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) independent of procedural success.

CONVENTIONAL CVD RISK FACTORS

Lifestyle and diet

Few data are available regarding the independent contribution of diet and lifestyle factors on the acceleration of CVD in patients with CKD. However, given the clustering of risk factors associated with obesity and type 2 diabetes, one would expect that a sedentary lifestyle and/or poor dietary habits, including an excessive intake of sugars, simple carbohydrates, and saturated fats, would be common among patients with, at a minimum, early diabetic CKD. Weight reduction has been shown to notably improve blood glucose control and, in some cases, result in the apparent resolution of diabetes as it is currently defined. Moreover, exercise training programmes can improve the conventional cardiac risk profile of renal transplant recipients.[w3–5] Although there have been no prospective, comparative studies of diet and lifestyle changes on CVD outcomes in patients with CKD, normalisation of body weight and fat stores, reduction in sodium intake, and regular aerobic exercise would be expected to have a salutary impact on this escalating patient population (table 1). Given the expected higher rates of novel risk factors including endothelial dysfunction, oxidative stress, and inflammation, intensive lifestyle modification, including dietary changes and regular aerobic exercise, may reduce the incidence of CVD in this population.

Hypertension

The renin–angiotensin system (RAS) and sympathetic nervous system are aberrantly activated, resulting in increased afterload, left ventricular enlargement, greater myocardial oxygen consumption, and augmented sheer stress at the endothelial level in patients with CKD. Opportunities for modulation of the RAS within the vascular tree occur at several points (fig 2).

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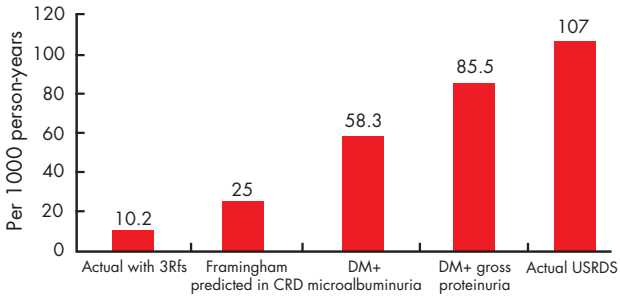

Figure 1 Risk of coronary heart disease death by gradations of chronic kidney disease (CRD) and diabetes (DM). Adapted from Levin A, Steven L, McCullough PA. Cardiovascular disease and the kidney. Tracking a killer in chronic kidney disease. *Postgrad Med* 2002;**111**:53–60.

Additionally, many CKD patients with hypertension develop left ventricular hypertrophy, resulting in an increased myocardial mass to endothelial surface area, and an unfavourable myocardial oxygen supply and demand relation. Hyperactivation of the RAS leads to expression of oxidised low density lipoprotein receptors and acceleration of atherosclerosis (fig 3). As eGFR declines, systemic blood pressure rises causing greater sheer stress, increased risk of plaque rupture, and episodic coronary occlusion. Consequently, blood pressure control to a target systolic blood pressure < 130 mm Hg (ideally < 120 mm Hg) is currently recommended (table 1).

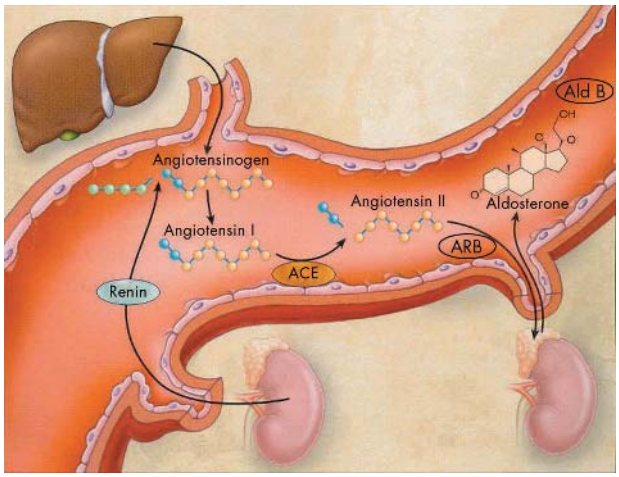

Figure 2 Angiotensinogen is secreted by the liver and is cleaved by renin, which is secreted into the lumen of renal afferent arterioles by juxtaglomerular cells. Angiotensin I is then converted to angiotensin II by angiotensin converting enzyme, primarily in endothelial cells. In the zona glomerulosa of the adrenal cortex, angiotensin II stimulates the production of aldosterone. Aldosterone production is also stimulated by potassium, corticotropin, catecholamines (for example, noradrenaline (norepinephrine)), and endothelins. Points of therapeutic impact are shown as ACE (angiotensin converting enzyme inhibition), ARB (angiotensin II receptor blockade), and AldB (aldosterone receptor blockade). Adapted from Weber KT. Aldosterone in congestive heart failure. *N Engl J Med* 2001;**345**:1689–97.

Table 1 Primary and secondary cardiovascular disease prevention strategies for patients with chronic kidney disease

Preventive measure	Rationale
Generally accepted	
Weight loss/weight maintenance at BMI ⩽25 kg/m^2	Resolution of the dysmetabolic syndrome Prevention of/improvement in diabetes
Aerobic exercise/strength training 30 min/day most days of the week	Primary/secondary prevention of MI, stroke, and CVD death Improvement in other risk factors in CKD patients
Low sodium intake	Reduce blood pressure Make blood pressure more responsive to medications
Avoidance of NSAIDS	Reduced risk of superimposed NSAID nephropathy Reduced risk of fluid retention and heart failure
Aspirin 81 mg by mouth, four times daily	Primary/secondary prevention of MI and stroke
Lipid control (diet, statin, fibrates, niacin, others)	Primary/secondary prevention of MI, stroke, and CVD death
LDL-C <2.6 mmol/l TG <1.7 mmol/l HDL-C >1.3 mmol/l	Possible reduction in progression of CKD
Blood pressure control to optimal target of SBP <120 mm Hg	Primary/secondary prevention of MI, stroke, heart failure, and CVD death
RAS blocking agents Add-on treatment	Reduce/normalise microalbuminuria Slow the progression to ESRD and death
Blood glucose control in diabetes to target glycohaemoglobin <7%	Reduction in risk of MI, stroke, and CVD death Reduction in worsened nephropathy/ retinopathy
Experimental—limited supportive evidence	
Reduce/normalise Lp(a) <1.1 mmol/l Niacin Lipid apheresis	Possible primary/secondary prevention of MI, stroke, and CVD death
Folic acid, B12, B6 supplementation to normalise (<14 μmol/l) Hcy	Primary/secondary prevention of MI, stroke, and CVD death
Sevelamer for combined phosphate and LDL-C lowering in advanced CKD and ESRD	Attenuation of progression of coronary calcification by EBCT
Vitamin E 800 IU by mouth, four times daily in ESRD	Reduce composite CVD events
NAC 600 mg by mouth, twice daily in ESRD	Reduce composite CVD events

BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; EBCT, electron beam computed tomography; ESRD, end stage renal disease; Hcy, homocysteine; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; NAC, N-acetylcysteine; NSAIDS, non-steroidal anti-inflammatory drugs; RAS, renin–angiotensin system; SBP, systolic blood pressure; TG, triglycerides.

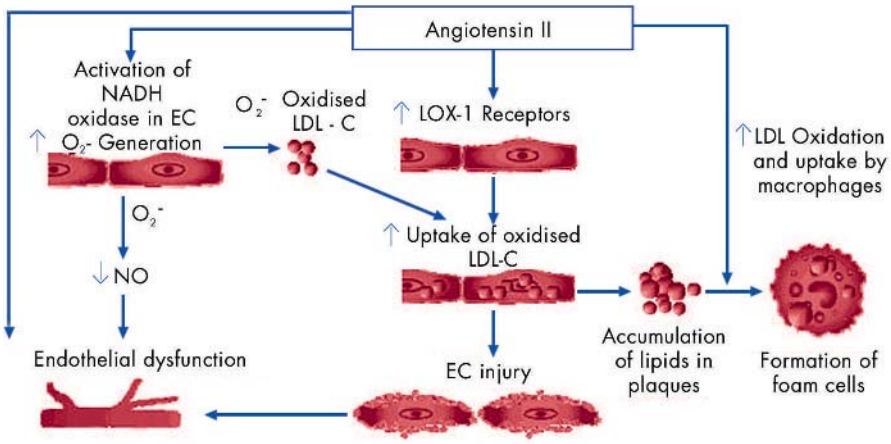

Figure 3 The renin–angiotensin system, creating the formation of angiotensin II, directly upregulates oxidised low density lipoprotein receptors on the endothelium and accelerates the progression of coronary atherosclerosis. EC, endothelial cell; LDL-C, low density lipoprotein cholesterol; LOX-1, oxidised low density lipoprotein receptor; NADH, nicotinamide adenine dinucleotide; NO nitric oxide.

Diabetes mellitus

Over 40% of end stage renal disease (ESRD) is secondary to diabetic nephrosclerosis,[w6] and 48–57% of patients with diabetes mellitus (DM) have overt diabetic nephropathy.[1] Patients with diabetes have significantly raised concentrations of serum insulin, a potent growth factor for atherosclerosis, in addition to a dyslipidaemic state. The epidemic of diabetes so measurably impacts CVD that the most recent National Cholesterol Education Program adult treatment panel guidelines listed DM as a CVD equivalent, and recommend treating afflicted patients accordingly.[w7] In those with excess adiposity and type 2 diabetes, weight reduction is the intervention of choice to improve or resolve the diabetic condition. Optimal glycaemic control (glycohaemoglobin $< 7\%$) has been shown to reduce microvascular events (retinopathy) and, along with blood pressure lowering, decrease the incidence of macrovascular events (myocardial infarction, stroke, and CVD death) in patients with type 1 or type 2 diabetes.

Dyslipidaemias

Dyslipidaemias occur in up to 67% of CKD patients.[w8] This patient population often demonstrates diminished concentrations of cardioprotective high density lipoprotein cholesterol (HDL-C), and atherogenic increases in triglycerides and low density lipoprotein cholesterol (LDL-C). In particular, CKD patients have heightened concentrations of apolipoproteins AIV and B48. Furthermore, uraemic stress results in increased concentrations of oxidised LDL-C, a highly reactive and atherogenic species. Thus, it appears that hyperactivation of the RAS, raised insulin concentrations, and the dyslipidaemia of CKD work in concert to advance atherosclerosis at faster rates than in those with preserved renal function. Current guidelines support the lipid targets given in table 1.

Abbreviations

ACE: angiotensin converting enzyme
CABG: coronary artery bypass grafting
CKD: chronic kidney disease
Cr: serum creatinine
CRP: C reactive protein
CVD: cardiovascular disease
DM: diabetes mellitus
eGFR: estimated glomerular filtration rate
ESRD: end stage renal disease
Hcy: homocysteine
IL-6: interleukin-6
HDL-C: high density lipoprotein cholesterol
LDL-C: low density lipoprotein cholesterol
Lp: lipoprotein
PCI: percutaneous coronary intervention
RAS: renin–angiotensin system
RRT: renal replacement therapy
TGF-β1: transforming growth factor beta 1

NOVEL CORONARY DISEASE RISK FACTORS

Homocysteinaemia

Homocysteine (Hcy), a product of methionine metabolism, is increased two- to fourfold in patients with CKD,[w9] as renal tubular excretion normally accounts for 70% of Hcy clearance. When the eGFR drops below 60 ml/min/1.73 m^2, Hcy is predictably raised. Furthermore, mean Hcy concentrations are increased 14–20% in ESRD patients with CVD compared to those without.[5 6] Patients with raised Hcy concentrations have a three- to fourfold increased CVD event rate[5 w10] and a 10.9-fold increased cerebrovascular event rate.[w11] Hcy values inversely correlate with red blood cell folate concentrations. Accordingly, supratherapeutic doses of folic acid (5–20 mg daily) and vitamin B12, both components of Hcy metabolism, may decrease Hcy concentrations by 20–55% in ESRD patients.[w12 w13] One trial showed that N-acetylcysteine, a potent antioxidant, may acutely lower plasma Hcy concentrations in this patient population.[w14]

Lipoprotein (a)

Lipoprotein Lp(a) concentrations are increased 43% in patients on RRT as compared with the general population.[7] In addition, CKD patients have higher concentrations of the low molecular weight isoforms, which have even more pronounced atherogenic characteristics.[w15] Lp(a) is raised in 64% of RRT patients with CVD in contrast to 3.8% of those without.[8] The putative atherogenic mechanism of Lp(a) includes macrophage foam cell production, inhibition of fibrinolysis, and adverse effects on endothelial dependent vascular reactivity.[7] Preliminary studies demonstrate that Lp(a) concentrations may be reduced with niceritrol (a niacin prodrug), plasma apheresis, and renal transplantation.[w16 w17]

Oxidative stress

Patients with CKD and ESRD experience significant oxidative stress manifested by abundant glycosylation products and oxidised proteins such as LDL-C. Oxidative stress has profound atherogenic effects as reactive oxygen species combine with nitric oxide resulting in endothelial dysfunction. Preliminary studies in ESRD patients have demonstrated that N-acetylcysteine decreases the concentrations of oxidised LDL-C by 76%, and the composite end points of non-fatal myocardial infarction, cardiovascular death, revascularisation, and ischaemic stroke by 40%. While antioxidants have not reduced CVD events in the general population, two clinical trials of antioxidant use in ESRD patients reported reductions in morbidity and mortality.[9 10] Additional clinical trials in this population are warranted.

Endothelial dysfunction

Patients with CKD have increased concentrations of asymmetric dimethyl arginine, a nitric oxide synthase inhibitor, and correspondingly diminished concentrations of nitric oxide, a potent coronary vasodilator and an important local factor in endothelial function.[w18] Other aberrancies of CKD include raised endothelin production and reduced thrombomodulin expression.[w18] The end result is impairment of coronary flow reserve and the myocardial microcirculation. Hyperactivation of the RAS further negates the actions of nitric oxide, inhibiting endothelium dependent vasodilation, and hastening the inexorable progression of coronary disease (fig 4).

Transforming growth factor

Transforming growth factor beta 1 (TGF-β1) is implicated in the pathogenesis of diabetic nephropathy. TGF-β1 is an anti-inflammatory cytokine that may show some repair or protective effects in atherosclerosis. In ESRD patients, serum concentrations of TGF-β1 are reduced as compared with the general population, and may result in accelerated atherosclerosis. TGF-β1 values are reduced in CKD patients with CVD or peripheral arterial disease. Furthermore, patients with triple vessel coronary artery disease have even greater reductions of serum TGF-β1. For every 1 ng/ml decrease in TGF-β1 there is a corresponding increase (~9%) in the CVD event rate.[11]

Chronic inflammation

Trauma, infection, and inflammation may result in increased serum concentrations of positive acute phase reactants such as C reactive protein (CRP), fibrinogen, ferritin, interleukin-6 (IL-6) and Lp(a). In addition, there is a corresponding decrease in negative acute phase reactants such as albumin, prealbumin, cholesterol, and apolipoprotein A1 and B. IL-6 potently induces hepatic synthesis of CRP, which binds to the Fc-receptor of the immunoglobulin protein, and subsequently activates the complement cascade. Chronic inflammation commonly occurs in ESRD as a result of intercurrent illnesses such as glomerulonephritis and infection, as well as RRT specific factors, including exposure to water born endotoxins and bioincompatible dialysis membranes.[w19] A raised serum CRP value is the most powerful predictor of mortality in patients on RRT and portends a 4.6-fold increased risk of CVD death.[w20] In addition to abnormal CRP concentrations, ESRD patients are 16.6-fold more likely to have raised fibrinogen concentrations as part of the acute phase response,[w20] which may result in increased plasma viscosity, endothelial injury, and thrombosis. Plasma apheresis has been shown to effectively reduce the acute phase reactant fibrinogen in ESRD patients. While inflammatory factors may be slightly raised in those with normal renal function, they are disproportionately high in CKD and should be treated with aspirin and statins.

Vascular calcification

Patients on RRT have coronary calcification scores far exceeding those of the general population, including those found in younger patients. Coronary calcification as measured by computed tomography is present in 88% of ESRD patients between the ages of 20–30 years in contrast to 5% of age matched controls.[12] In addition, serum calcium and phosphate concentrations as well as the calcium–phosphate product significantly impact vascular calcification. ESRD patients on non-calcium based phosphate binders are less likely to have vascular calcification within the coronary arteries (0 *v* 37%, $p = 0.03$) and thoracic aorta (0 *v* 75%, $p = 0.01$) after a 52 week follow up period as compared with ESRD patients on calcium based phosphate binders.[13] While vascular calcification cannot be reversed with current treatments, it appears that LDL-C reduction with sevelamer and statins attenuates progression in humans. Although a

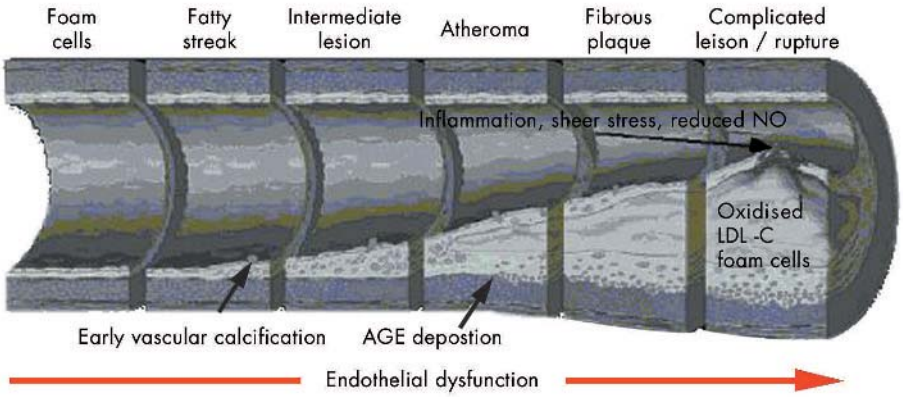

Figure 4 Processes related to the acceleration of coronary disease and plaque rupture in patients with renal disease. AGE, advanced glycation end products; LDL-C, low density lipoprotein cholesterol; NO, nitric oxide.

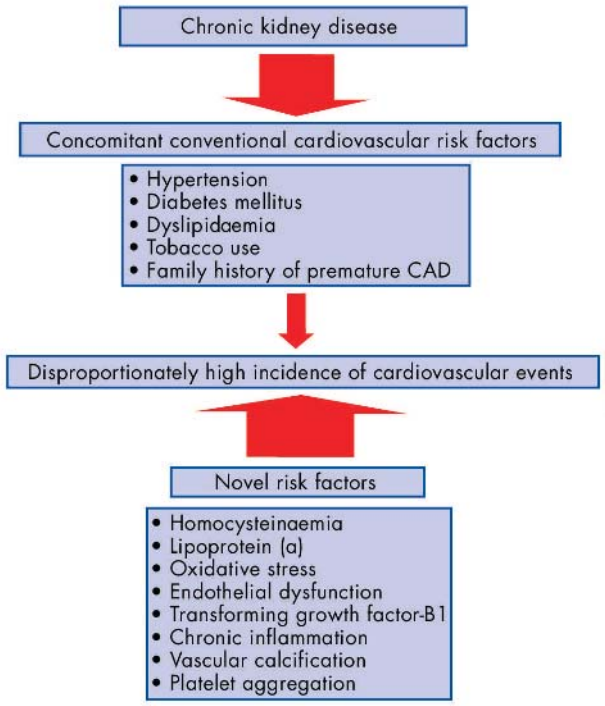

Figure 5 The disproportionately increased rates of coronary artery disease are caused in part by an excess burden of novel cardiovascular risk factors. CAD, coronary artery disease.

controversial topic, future randomised trials of phosphate lowering and lipid manipulation with measurement of vascular calcification are clearly needed.

Platelet aggregation

In ESRD patients, exposure to heparin, bioincompatible dialysis membranes, and arteriovenous shunts may result in increased platelet aggregation.[14 w21] Similar effects on platelet aggregation have been shown in chronic ambulatory peritoneal dialysis patients and CKD patients with hypertriglyceridaemia.[w22] Nonetheless, many CKD patients at risk for CVD do not receive antiplatelet treatment because of concerns over platelet dysfunction and the potential for bleeding complications. The combination of excess thrombin generation and decreased platelet aggregability make the patient with CKD at risk, simultaneously, for thrombotic events and haemorrhage. In general, low dose daily aspirin is recommended for those with CKD, since it is considered a CVD risk equivalent state.

Cardioprotective treatments

Studies have consistently shown that CKD patients presenting with acute myocardial infarction are less likely to receive standard treatments. For example, ESRD patients are less likely to receive cardioprotective medications such as aspirin, heparin, β blockers, and angiotensin converting enzyme (ACE) inhibitors, and are 51% less likely to receive reperfusion therapy for acute myocardial infarction as compared with patients with normal renal function.[10 15–17] In general, patients with CKD have a greater relative risk reduction with aspirin, β blockers, ACE inhibitors, glycoprotein IIb/IIIa inhibitors, and lipid lowering treatment as compared with the general population after an acute coronary event. Efforts should be made to improve the quality of medical care to coronary patients with CKD, and future randomised trials of contemporary treatments should target this at-risk population.

Renal dysfunction and acceleration of coronary disease: key points

- Patients with renal disease have a high prevalence of CVD and a corresponding high incidence of CVD events
- Novel CVD risk factors such as homocysteinaemia, raised Lp(a), oxidative stress, endothelial dysfunction, decreased concentrations of TGF-β1, chronic inflammation, and vascular calcification appear to play an escalating role in the accelerated rates of atherogenesis in CKD patients
- Efforts should be made to improve the quality of medical care to coronary patients with CKD

CLINICAL OUTCOMES FOLLOWING CORONARY REVASCULARISATION

CKD significantly impacts clinical outcomes following coronary revascularisation procedures. Even in patients with angiographically successful PCI, adverse clinical events have been shown to increase exponentially with graded declines in eGFR.[18–20 w23] The Mayo Clinic reported the following one year mortality rates stratified according to renal function: 1.5% (eGFR ⩾ 70 ml/min), 3.6% (eGFR 50–69 ml/min), 7.8% (eGFR 30–49 ml/min), and 18.3% (eGFR < 30 ml/min).[18] With saphenous vein graft intervention, inferior clinical outcomes in CKD patients are reported, with one year mortality rates of 7.1% (eGFR ⩾ 70 ml/min), 8.0% (eGRF 50–69 ml/min), 19.0% (eGFR 30–49 ml/min), and 36.7% (eGFR < 30 ml/min).[19] Clinical outcomes in CKD patients following CABG are poorer as well with an in-hospital mortality of 1.6% (serum creatinine (Cr) < 88.4 mmol/l), 5.9% (Cr ⩾ 132.6 mmol/l), and 11% (maintenance haemodialysis).[w24] Actuarial 10 year survival remains dismal in CKD following surgical revascularisation with survival rates of 87% (Cr < 88.4 mmol/l), 32% (Cr ⩾ 132.6 mmol/l), and 29% (maintenance haemodialysis).[w24] However, bilateral internal thoracic artery grafting has been associated with notable improvement in survival for CKD patients (100%, n = 23).[w24] Thus, CKD confers an exponential increase in major adverse cardiac events following PCI and CABG, which may be offset by arterial graft revascularisation.

CONCLUSION

Patients with renal disease have a high prevalence of CVD and its associated sequelae, which may be partially explained by conventional CVD risk factors such as hypertension, diabetes mellitus, and dyslipidaemia. Thus, aggressive treatment of these risk factors with diet, exercise, weight reduction, and drug treatment should reduce the CVD burden in CKD patients to some extent. Nevertheless, conventional risk factors per se cannot fully explain the prevalence of CVD in this patient population (fig 5). Novel CVD risk factors such as homocysteinaemia, raised Lp(a), oxidative stress, endothelial dysfunction, decreased concentrations of TGF-β1, chronic inflammation, and vascular calcification appear to play an escalating role in the accelerated rates of atherogenesis in these patients. Understanding the mechanisms behind novel CVD risk factors and how to modify them favourably may allow us to attenuate the high incidence of non-fatal and fatal cardiovascular events in patients with CKD. In addition,

CKD confers inferior clinical outcomes following successful PCI and CABG. Aggressive risk factor modification, preventive treatments, and arterial graft revascularisation may result in improved outcomes.

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REFERENCES

1 **McCullough PA**. Cardiorenal risk: an important clinical intersection. *Rev Cardiovasc Med* 2002;**3**:71–6.
2 **Luke RG**. Chronic renal failure—a vasculopathic state. *N Engl J Med* 1998;**339**:841–3.
3 **Foley RN**, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 1998;**9**:S16–23.
► **This review article succinctly characterises the significantly (10- to 20-fold) increased cardiovascular mortality in haemodialysis patients which is out of proportion to the presence of traditional risk factors.**
4 **Cheung AK**, Sarnak MJ, Yan G, *et al*. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. *Kidney Int* 2000;**58**:353–62.
► **This cross sectional analysis of the first 1000 patients enrolled in the National Institutes of Health hemodialysis study establishes that traditional risk factors alone cannot account for the degree of cardiovascular morbidity in patients with chronic kidney disease.**
5 **Manns BJ**, Burgess ED, Hyndman ME, *et al*. Hyperhomocyst(e)inemia and the prevalence of atherosclerotic vascular disease in patients with end-stage renal disease. *Am J Kidney Dis* 1999;**34**:669–77.
► **Patients in the quartile with the highest serum homocysteine values had the greatest prevalence of coronary artery disease. This hypercoagulable state in chronic kidney disease patients may potentially be attenuated with supplemental folic acid.**
6 **Robinson K**, Gupta A, Dennis V, *et al*. Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and is closely linked to plasma folate and pyridoxine concentrations. *Circulation* 1996;**94**:2743–8.
7 **Bostom AG**, Shemin D, Lapane KL, *et al*. Hyperhomocysteinemia, hyperfibrinogenemia, and lipoprotein (a) excess in maintenance dialysis patients: a matched case-control study. *Atherosclerosis* 1996;**125**:91–101.
► **This well thought out case–control study demonstrates that haemodialysis patients have multiple serum abnormalities which greatly increase the cardiovascular event rate even after adjusting for traditional risk factors.**
8 **Docci D**, Manzoni G, Bilancioni R, *et al*. Serum lipoprotein(a) and coronary artery disease in uremic patients on chronic hemodialysis. *Int J Artif Organs* 1994;**17**:41–5.
► **In this single centre study, haemodialysis patients were found to have raised lipoprotein(a) concentrations compared to controls. Furthermore, raised concentrations had a strong association with concomitant coronary artery disease.**
9 **Tepel M**, van der Giet M, Statz M, *et al*. The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized, controlled trial. *Circulation* 2003;**107**:992–5.
► **Oxidative stress plays a significant role in formation of atherosclerotic plaques in chronic kidney disease patients. This randomised clinical trial demonstrates that acetylcysteine treatment may significantly lower the cardiovascular event rate.**
10 **Boaz M**, Smetana S, Weinstein T, *et al*. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. *Lancet* 2000;**356**:1213–8.
11 **Stefoni S**, Cianciolo G, Donati G, *et al*. Low TGF-beta1 serum levels are a risk factor for atherosclerosis disease in ESRD patients. *Kidney Int* 2002;**61**:324–35.
► **Transforming growth factor β-1 may inhibit atherogenesis. In this prospective study of haemodialysis patients, TGF β-1 proves to be an independent predictor of significant coronary artery disease. Small reductions in serum TGF β-1 concentrations corresponded to a pronounced increase in cardiovascular mortality.**
12 **Goodman WG**, Goldin J, Kuizon BD, *et al*. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;**342**:1478–83.
13 **Chertow GM**, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002;**62**:245–52.
► **This randomised clinical trial supports the role of calcium metabolism in the atherogenic process of chronic kidney disease patients, and offers a potential treatment modality to alter calcium homeostasis and retard vascular calcification.**
14 **Aggarwal A**, Kabbani SS, Rimmer JM, *et al*. Biphasic effects of hemodialysis on platelet reactivity in patients with end-stage renal disease: a potential contributor to cardiovascular risk. *Am J Kidney Dis* 2002;**40**:315–22.
► **This prospective trial proves that there is increased platelet reactivity early in dialysis which may place patients at greater risk for acute thrombotic events such as myocardial infarction or stroke.**
15 **Beattie JN**, Soman SS, Sandberg KR, *et al*. Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis* 2001;**37**:1191–200.
► **This important paper reveals that patients with chronic kidney disease are less likely to receive standard treatments in the setting of myocardial infarction compared to those with normal renal function.**
16 **Freeman RV**, Mehta RH, Al Badr W, *et al*. Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. *J Am Coll Cardiol* 2003;**41**:718–24.
17 **Wright RS**, Reeder GS, Herzog CA, *et al*. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med* 2002;**137**:563–70.
18 **Best PJ**, Lennon R, Ting HH, *et al*. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol* 2002;**39**:1113–9.
19 **Best PJ**, Holmes DR Jr. Chronic kidney disease as a cardiovascular risk factor. *Am Heart J* 2003;**145**:383–6.
20 **Naidu SS**, Selzer F, Jacobs A, *et al*. Renal insufficiency is an independent predictor of mortality after percutaneous coronary intervention. *Am J Cardiol* 2003;**92**:1160–4.

Additional references appear on the *Heart* website—http://www.heartjnl.com/supplemental

1. Collins AJ, Li S, Ma JZ, *et al*. Cardiovascular disease in end-stage renal disease patients. *Am J Kidney Dis* 2001;**38**:S26–S29.

2. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;**32**:S112–S119.

3. Painter PL, Hector L, Ray K, *et al*. Effects of exercise training on coronary heart disease risk factors in renal transplant recipients. *Am J Kidney Dis* 2003;**42**:362–9.

4. DePaul V, Moreland J, Eager T, *et al*. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial. *Am J Kidney Dis* 2002;**40**:1219–29.

5. Laukkanen JA, Kurl S, Salonen JT. Cardiorespiratory fitness and physical activity as risk predictors of future atherosclerotic cardiovascular diseases. *Curr Atheroscler Rep* 2002;**4**:468–76.

6. Prichard S. Risk factors for coronary artery disease in patients with renal failure. *Am J Med Sci* 2003;**325**:209–13.

7. Anonymous. Changes in ATP III focus on diabetes and the metabolic syndrome. *Am J Manag Care* 2002;(Suppl Symposium Reporter):1, 6.

8. Avram MM, Fein PA, Antignani A, *et al*. Cholesterol and lipid disturbances in renal disease: the natural history of uremic dyslipidemia and the impact of hemodialysis and continuous ambulatory peritoneal dialysis. *Am J Med* 1989;**87**:55N–60N.

9. Bachmann J, Tepel M, Raidt H, *et al*. Hyperhomocysteinemia and the risk for vascular disease in hemodialysis patients. *J Am Soc Nephrol* 1995;**6**:121–5.

10. Bostom AG, Shemin D, Verhoef P, *et al*. Elevated fasting total plasma homocysteine levels and cardiovascular disease outcomes in maintenance dialysis patients. A prospective study. *Arterioscler Thromb Vasc Biol* 1997;**17**:2554–8.
11. Abdel-Raheem MM, Hebert B, Potti A, *et al*. Hyperhomocysteinemia and the risk of thromboembolic phenomenon in patients with chronic renal failure. *Thromb Res* 2002;**105**:299–302.
12. Bostom AG, Shemin D, Lapane KL, *et al*. High dose-B-vitamin treatment of hyperhomocysteinemia in dialysis patients. *Kidney Int* 1996;**49**:147–52.
13. Wilcken DE, Dudman NP, Tyrrell PA, *et al*. Folic acid lowers elevated plasma homocysteine in chronic renal insufficiency: possible implications for prevention of vascular disease. *Metabolism* 1988;**37**:697–701.
14. Bostom AG, Shemin D, Yoburn D, *et al*. Lack of effect of oral N-acetylcysteine on the acute dialysis-related lowering of total plasma homocysteine in hemodialysis patients. *Atherosclerosis* 1996;**120**:241–4.
15. Kronenberg F, Neyer U, Lhotta K, *et al*. The low molecular weight apo(a) phenotype is an independent predictor for coronary artery disease in hemodialysis patients: a prospective follow-up. *J Am Soc Nephrol* 1999;**10**:1027–36.
16. Black IW, Wilcken DE. Decreases in apolipoprotein(a) after renal transplantation: implications for lipoprotein(a) metabolism. *Clin Chem* 1992;**38**:353–7.
17. Nakahama H, Nakanishi T, Uyama O, *et al*. Niceritrol reduces plasma lipoprotein(a) levels in patients undergoing maintenance hemodialysis. *Ren Fail* 1993;**15**:189–93.

18. Becker BN, Himmelfarb J, Henrich WL, *et al*. Reassessing the cardiac risk profile in chronic hemodialysis patients: a hypothesis on the role of oxidant stress and other non-traditional cardiac risk factors. *J Am Soc Nephrol* 1997;**8**:475–86.
19. Panichi V, De Pietro S, Andreini B, *et al*. Cytokine production in haemodiafiltration: a multicentre study. *Nephrol Dial Transplant* 1998;**13**:1737–44.
20. Westhuyzen J, Healy H. Review: Biology and relevance of C-reactive protein in cardiovascular and renal disease. *Ann Clin Lab Sci* 2000;**30**:133–43.
21. Viener A, Aviram M, Better OS, *et al*. Enhanced in vitro platelet aggregation in hemodialysis patients. *Nephron* 1986;**43**:139–43.
22. Sabo RS, Bartoli F, Apitz-Castro R. In vivo platelet hyperreactivity, another risk factor for patients under continuous ambulatory peritoneal dialysis. *Nephron* 1988;**49**:228–30.
23. Rubenstein MH, Sheynberg BV, Harrell LC, *et al*. Effectiveness of and adverse events after percutaneous coronary intervention in patients with mild versus severe renal failure. *Am J Cardiol* 2001;**87**:856–60.
24. Nakayama Y, Sakata R, Ura M, *et al*. Long-term results of coronary artery bypass grafting in patients with renal insufficiency. *Ann Thorac Surg* 2003;**75**:496–500.